RAPID COMMUNICATION

Dietary factors associated with plasma high molecular weight and total adiponectin levels in apparently healthy women

Mary Yannakoulia¹, Nikos Yiannakouris², Labros Melistas¹, Evaggelia Fappa¹, Nikoletta Vidra¹, Meropi D Kontogianni¹ and Christos S Mantzoros³

Departments of ¹Nutrition and Dietetics and ²Home Economics and Ecology, Harokopio University, Athens 17671, Greece and ³Division of Endocrinology, Diabetes and Metabolism, ST 816, Department of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center (BIDMC), 330 Brookline Avenue, Boston, Massachusetts 02215, USA

(Correspondence should be addressed to C S Mantzoros; Email: cmantzor@bidmc.harvard.edu)

Abstract

Objective: Our aim was to investigate associations between dietary factors and high molecular weight (HMW) as well as total adiponectin in a sample of apparently healthy adult Mediterranean women.

Design and methods: Two hundred and twenty women were enrolled in this study. Anthropometric and body composition measurements were performed in all subjects. Fasting blood samples were taken; HMW and total adiponectin concentrations were measured. Food intake was evaluated using 3-day food records. The frequency of consumption of several food groups was approximately quantified in terms of number of servings per day. Furthermore, dietary intakes of betaine, choline, and free choline were estimated.

Results: Women in the highest HMW adiponectin tertile had higher fruit intake compared with those with lower levels, after adjusting for potential confounders ($P=0.04$). On the contrary, dietary betaine and choline intakes were not different among HMW adiponectin tertiles. In linear models, fruit consumption, controlling for biological and lifestyle variables, was significantly related to HMW adiponectin (partial $r=0.15$, $P=0.04$), but the association with total adiponectin did not reach statistical significance (partial $r=0.11$, $P=0.12$). A significant negative correlation between total adiponectin and refined cereals was also observed (partial $r=-0.16$, $P=0.03$).

Discussion: This is the first study that evaluates associations between dietary factors and HMW adiponectin levels. The associations found are moderate and indicate that, after multivariate adjustment, fruit consumption is related to HMW adiponectin in both linear and nonlinear models.

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Introduction

Adiponectin, an insulin-sensitizing hormone secreted by adipose tissue, has been shown to affect glucose and lipid metabolism and to exert distinct anti-atherogenic, anti-diabetogenic, and anti-inflammatory actions (1). Adiponectin circulates in plasma in the form of a low molecular weight trimer, a middle molecular weight hexamer, and a high molecular weight (HMW) 12- to 18-mer (2). It has been proposed that HMW, rather than total adiponectin, might be more closely associated with insulin resistance (IR) and the presence of metabolic syndrome (3, 4). There is also, however, evidence indicating that the predictive value of HMW over total adiponectin in assessing metabolic parameters may not be appreciably different from the clinical point of view (5). Modifiable lifestyle factors, including diet-related parameters, have been associated with the physiological regulation of plasma adiponectin levels. Although no association has been found between serum adiponectin levels and total energy or macronutrient intake (6),

significant, albeit weak, associations have been detected with specific food groups. Whole-grain cereals, dietary cereal fiber intake, and moderate alcohol consumption (40 g/day) have been positively associated with higher plasma adiponectin concentrations in Western populations (7, 8). It remains unknown, though, whether and to what extent HMW adiponectin is associated with dietary factors since no prior study has focused on HMW adiponectin. Furthermore, it has been recently proposed that dietary betaine and choline intake are positively associated with inflammatory markers, including C-reactive protein, interleukin-6, and tumor necrosis factor- α , after multivariate adjustment for various demographic, clinical, and lifestyle characteristics in a sample of apparently healthy Greek adults (9). Although adiponectin counteracts the proinflammatory effects of tumor necrosis factor- α and IL-6 inhibits adiponectin expression and secretion in adipocytes (10), associations between the above dietary components and total or HMW adiponectin levels have not been evaluated. Thus, our aim was to investigate

associations between several dietary factors and total as well as HMW adiponectin in a sample of apparently healthy adult Mediterranean women.

Subjects and methods

Subjects

Two hundred and twenty Greek women (mean age, 48.3 ± 12.3 years; age range 18–84 years) were consecutively enrolled in this study. Women were recruited through local advertisement. None of them was referred directly by a physician. Although study subjects reported no known history of diabetes, we found two of them with fasting glucose levels higher than 126 mg/dl. Furthermore, 7 subjects were taking medication (corticosteroids, lipid-lowering drugs, or other drugs) and 15 were on a weight-reducing diet. The study protocol was approved by the Ethics Committee of Harokopio University; all subjects were informed on the purpose and procedures of the study and signed a consent form. They provided demographic, medical, and lifestyle information, including dietary, physical activity, and smoking habits. A fasting blood sample was taken from all participants who also underwent anthropometric and body composition measurements. With regard to menstruation status, they were classified as premenopausal if they had regular menses, perimenopausal if they were suffering from irregular menses, and postmenopausal if they had ceased menstruating for at least 12 months.

Body composition

Body composition was evaluated in all subjects using dual-energy X-ray absorptiometry whole-body scanner (Model DPX+; Lunar Corp., Madison, WI, USA). Anthropometric measurements were also performed, namely body weight, height, waist, and hip circumferences. Body mass index (BMI) was calculated as kg/m^2 .

Dietary assessment

Dietary intake of the 220 participants was assessed using 3-day food records. Subjects were asked to record type and amount of food and beverage consumed for two specific consecutive weekdays and one weekend day during the same week. Clear instructions were given to them on how to record the quantity of food eaten using standard household and other measures. The frequency of consumption of several food groups was approximately quantified in terms of number of servings per day. The food groups assessed were the core food groups of the traditional Greek diet, as depicted in the Mediterranean diet pyramid and the dietary guidelines for the Greek population (11). For the present analysis, however, only food groups assumed to be consumed on a daily basis were used, namely fruits and vegetables, dairy products (low

and full fat), and cereals (nonrefined and refined). Dietary intakes of betaine, choline, and free choline were calculated based on the food values provided by the US Department of Agriculture. Low-energy reporting was evaluated for each subject using the ratio of the energy intake/basal metabolic rate (EI/BMR). BMR was estimated by the Schofield equations that have been adopted by the 2004 Food and Agriculture Organization (FAO)/WHO/United Nations University (UNU) report (12). Participants with $\text{EI/BMR} < 1.04$ were classified as 'low-energy reporters', whereas those with $\text{EI/BMR} \geq 1.04$ 'normal energy reporters' or non-low-energy reporters (13).

Physical activity assessment

Assessment of physical activity was performed through a brief self-reported questionnaire (the Harokopio Physical Activity Questionnaire (HAPAQ)) that collects the previous week's self-reported physical activity (14). HAPAQ examines the time spent in light, moderate, and high-intensity activities and also requires sleeping to be recorded. The questionnaire is based on the metabolic equivalents of all activities of the previous week, including activities at work, leisure time, and rest or sleep, thus allowing the prediction of mean physical activity level (PAL).

Biochemical analysis

Blood samples were drawn after a 12-h fast between 0830 and 1030 h, and plasma was immediately frozen in -80°C until biochemical analysis. Plasma glucose concentrations and lipid profile were determined using commercially available enzymatic colorimetric assays (Alfa Wassermann BV, Woerden, The Netherlands) on an automated ACE analyzer (Schiapparelli Biosystems, Inc, Fairfield, NJ, USA). Plasma adiponectin and insulin concentrations were measured by RIA (adiponectin (Linco Research, St Charles, MO, USA): sensitivity 1 ng/ml, intraassay coefficient variation 1.78–6.21%; insulin (Diagnostics Systems Laboratory, Webster, TX, USA): sensitivity 1.3 $\mu\text{IU/ml}$, intraassay coefficient variation 4.5–8.3%). In addition, plasma levels of HMW adiponectin were determined using a novel ELISA test (Human Multimeric Adiponectin ELISA; ALPCO Diagnostics, Salem, NH, USA). The sensitivity of this assay was 0.05 ng/ml. IR was estimated using the homeostasis model assessment (HOMA-IR) with the following formula: $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{IU/ml}) \times \text{fasting glucose } (\text{mmol/l}) / 22.5$ (15).

Statistical analysis

Continuous variables are presented as mean $\pm$ s.d. and categorical variables as absolute frequencies. ANOVA was used for evaluating differences in the investigated outcomes across tertiles of HMW or total adiponectin.

We examined the potential role of dietary factors as predictors of HMW or total adiponectin concentrations using bivariate and multivariate models. Pearson and partial correlation coefficients were also calculated. All reported *P* values were based on two-tailed tests at a significance level of 5%. Statistical package for Social Sciences software, version 13.0 (SPSS Inc. 2003, Chicago, IL, USA), was used for all the statistical calculations.

Results

HMW and total adiponectin plasma levels were significantly correlated with anthropometric variables, namely BMI ($r = -0.20$, $P = 0.004$; $r = -0.18$, $P = 0.009$), waist circumference ($r = -0.23$, $P = 0.001$; $r = -0.21$, $P = 0.002$), and percent body fat ($r = -0.20$, $P = 0.004$; $r = -0.15$, $P = 0.025$), as well as with plasma glucose ($r = -0.18$, $P = 0.008$; $r = -0.20$, $P = 0.003$) and HOMA-IR ($r = -0.39$, $P < 0.001$; $r = -0.35$, $P < 0.001$). Clinical characteristics of the study population were examined according to HMW adiponectin tertiles (Table 1). Women in the highest tertile were older and had lower percent body fat and waist circumference. A trend

was also observed toward lower smoking rates among participants in the highest HMW adiponectin tertile; however, no statistically significant difference was observed between smokers and nonsmokers, including ex-smokers, with regard to HMW (5.0 ± 3.4 vs 5.7 ± 3.8 $\mu\text{g/ml}$, $P = 0.17$) and total adiponectin levels (15.6 ± 5.4 vs 16.7 ± 6.3 $\mu\text{g/ml}$, $P = 0.16$), even after controlling for age and anthropometric variables.

With regard to the dietary intake, a trend was observed toward higher fruit and lower full-fat dairy for those in the highest HMW adiponectin tertile. After adjustment for potential confounders (age, percent body fat, waist circumference, smoking status, PAL, menopausal status, and low-energy reporting), only the association with fruit intake became statistically significant ($P = 0.04$). Dietary betaine and choline intake were not different among HMW adiponectin tertiles.

When women were categorized according to their total adiponectin tertiles, associations observed with anthropometric variables were similar to those observed in the HMW adiponectin analysis. Furthermore, women in the lowest tertile of adiponectin levels had a higher percentage of energy from carbohydrates ($P = 0.03$) and lower from fat ($P = 0.02$), as well as higher total cereal intake ($P = 0.02$; data not shown). These correlations became nonsignificant after multivariate adjustment.

Table 1 Clinical and dietary characteristics of the study participants according to high molecular weight (HMW) adiponectin tertiles.

	Lowest tertile (<i>n</i> =75)	Medium tertile (<i>n</i> =72)	Highest tertile (<i>n</i> =73)	<i>P</i> for trend
HMW adiponectin ($\mu\text{g/ml}$)	2.2 ± 0.8	$4.7 \pm 0.8^{\dagger}$	$9.7 \pm 3.6^{\dagger, \$}$	< 0.001
Total adiponectin ($\mu\text{g/ml}$)	10.7 ± 4.1	$16.2 \pm 3.5^{\dagger}$	$21.7 \pm 4.5^{\dagger, \$}$	< 0.001
Clinical characteristics				
Age (years)	47.7 ± 11.7	45.9 ± 12.1	$50.9 \pm 12.4^{\ddagger}$	0.044
Postmenopausal (%)	52.7	45.1	57.7	0.314
Smokers (%)	42.7	50.7	31.5	0.063
BMI (kg/m^2)	29.9 ± 5.7	$26.9 \pm 4.6^*$	$27.1 \pm 5.1^*$	0.001
Overweight/obesity (%)	80	62*	60*	0.018
Body fat (%)	42.0 ± 6.7	$39.0 \pm 7.3^*$	$38.6 \pm 7.6^{*, \ddagger}$	0.009
Waist circumference (cm)	89.9 ± 11.3	$82.9 \pm 11.2^{\dagger}$	$82.2 \pm 12.1^{\dagger}$	< 0.001
Physical activity level	1.45 ± 0.21	1.47 ± 0.20	1.47 ± 0.21	0.871
Basal metabolic rate (Schofield equations, kcal/day)	1456 ± 155	$1405 \pm 150^*$	$1379 \pm 94^{\dagger}$	0.001
Dietary energy and macronutrient intake and low-energy reporting				
Total energy intake (E, kcal/day)	1603 ± 469	1601 ± 548	1520 ± 446	0.498
Carbohydrate (%E)	42.2 ± 7.0	41.3 ± 6.6	41.5 ± 8.5	0.720
Fat (%E)	41.2 ± 5.6	42.5 ± 6.0	42.2 ± 7.8	0.430
Protein (%E)	16.9 ± 3.5	16.2 ± 3.8	16.8 ± 3.5	0.517
Alcohol (%E)	1.4 ± 2.6	1.8 ± 3.2	1.2 ± 2.5	0.455
Low-energy reporting (%)	49	42	45	0.689
Food groups consumption				
Vegetables (servings/day)	1.5 ± 1.0	1.5 ± 1.2	1.4 ± 0.9	0.686
Fruits (servings/day)	1.2 ± 1.0	1.3 ± 1.0	1.6 ± 1.3	0.081
Nonrefined cereals (servings/day)	0.4 ± 0.8	0.5 ± 0.8	0.3 ± 0.6	0.221
Refined cereals (servings/day)	2.1 ± 0.3	2.5 ± 2.2	2.2 ± 1.9	0.102
Low-fat dairy (servings/day)	0.4 ± 0.6	0.3 ± 0.6	0.6 ± 0.8	0.117
Full-fat dairy (servings/day)	1.9 ± 1.4	2.1 ± 1.4	1.6 ± 1.3	0.060
Dietary betaine and choline intake				
Betaine (mg/day)	250.8 ± 192.3	195.7 ± 162.3	207.6 ± 199.9	0.198
Choline (mg/day)	219.3 ± 72.1	201.6 ± 73.1	211.5 ± 62.3	0.334
Free choline (mg/day)	54.8 ± 19.0	53.5 ± 18.8	51.8 ± 17.5	0.627

Data are presented as mean $\pm$ s.d. or frequencies. Comparisons versus the lowest tertile, Bonferroni corrected, * $P < 0.05$, $^{\dagger}P \leq 0.001$. Comparisons versus medium tertile, Bonferroni corrected, $^{\ddagger}P < 0.05$, $^{\$}P \leq 0.001$.

Associations between plasma levels of HMW or total adiponectin and selected food groups were also evaluated in linear models, before and after adjustment for the above-mentioned confounders (Table 2). In multivariate analysis, fruit consumption was significantly related to HMW adiponectin (partial $r=0.15$, $P=0.04$), but not significantly to total adiponectin (partial $r=0.11$, $P=0.12$), whereas a statistically significant negative correlation between total adiponectin and refined cereals was observed (partial $r=-0.16$, $P=0.03$). No statistically significant associations were found between HMW adiponectin and nonrefined cereal consumption (partial $r=-0.10$, $P=0.18$) or between total adiponectin and low-fat dairy consumption (partial $r=0.11$, $P=0.13$). The results did not change when the analysis was restricted to women not on a weight-reducing diet or those not taking medication and having normal blood glucose levels. After further exclusion of low-energy reporters, the associations remain of similar strength.

Discussion

The accumulating evidence supporting a role for adiponectin in improving IR and predicting cardiovascular risk factors generated significant interest on modifiable predictors of adiponectin levels, i.e., factors that could influence favorably or unfavorably its plasma concentrations. Moreover, since HMW adiponectin has been proposed to be the biologically more active form of the hormone, the identification of lifestyle factors that potentially influence its levels would be of clinical importance. This is the first study that evaluates associations between diet and both HMW and total adiponectin levels. The associations found are not particularly strong, but are similar in magnitude with those reported between total adiponectin and dietary factors (16). They indicate that, after multivariate adjustment, fruit consumption is significantly related to HMW adiponectin in both linear and nonlinear models; however, the association between fruits and total adiponectin levels was not statistically significant. Fruits have been previously related to total adiponectin, but also to other inflammatory markers and

cardiovascular risk factors (17, 18). Our results suggest that the beneficial metabolic effects of fruits may operate, in part, through associations with serum HMW adiponectin concentrations. This effect may be attributed to the biological, individual, or synergistic role of several nutritive and nonnutritive compounds of fruits. For example, Kuroyanagi *et al.* have reported that auraptene, found in citrus fruits, increases the levels of adiponectin mRNA and protein in adipocytes, as well as the ratio of the amount of HMW multimers of adiponectin to the total amount of adiponectin (19).

Furthermore, the weak, negative association between refined cereals and total adiponectin levels confirms previous findings on the negative association between glycemic index and adiponectin levels (8). No association was found between either dietary betaine or choline intake and HMW adiponectin, suggesting that the potential mechanisms linking these compounds with inflammation (9) may not be mediated by adiponectin levels.

Among the strengths of this study is the use of food records for evaluating subjects' dietary intake, including nutrient intake and food group consumption. Three-day food records provide quantitatively accurate information on food consumed during the investigated period: by recording food while it is consumed, the problem of reporting bias or omission is lessened, whereas subjects are not restricted to select from a predetermined list of foods included in the food frequency questionnaires. Furthermore, this method might provide much more meaningful information regarding short-term regulation of circulating hormone levels. Although plasma adiponectin levels do not vary markedly over longer periods of time in the absence of significant body weight changes (20), there may be a short-term biovariability. Short-term biovariability has been found to be twofold greater in healthy subjects than in those with the metabolic syndrome (21), and the present study has focused on healthy subjects.

The percentage of low-energy reporting in our sample, around 40%, may evoke some concern regarding potential bias. However, this proportion of low-energy reporters could be expected, as our sample consisted of a high percentage of middle-aged, overweight women; the literature points to a higher

Table 2 Pearson and partial correlation coefficients between high molecular weight (HMW) or total adiponectin and selected food groups.

	HMW adiponectin				Total adiponectin			
	<i>r</i>	<i>P</i>	<i>r</i> ²	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i> ²	<i>P</i>
Fruits	0.14	0.041	0.15	0.040	0.12	0.094	0.11	0.115
Refined cereals	−0.06	0.435	−0.05	0.491	−0.13	0.065	−0.16	0.028
Nonrefined cereals	−0.11	0.124	−0.10	0.183	−0.03	0.627	−0.02	0.794
Low-fat dairy	0.10	0.16	0.07	0.302	0.13	0.057	0.11	0.125
Full-fat dairy	0.01	0.959	0.03	0.653	−0.03	0.703	−0.03	0.642

r, Pearson correlation coefficients; *r*², partial correlation coefficients controlling for age, percent body fat, waist circumference, smoking status, physical activity level, menopausal status, and low-energy reporting.

proportion of low-energy reporting among female, older and overweight, subjects (22). On the other hand, existing evidence indicates that there are no differences in bread, potatoes, meat, or vegetable and fruit consumption between underreporters and other subjects (23), and that sweets and snacks are the mostly underreported food items (24, 25). Our study findings did not include these 'socially undesirable' foods; therefore, we believe that the associations reported herein were not influenced by the misreporting of dietary intake. Finally, to rule out conclusively any possible bias from this source, low-energy reporting was considered as a potential confounder in the additional multivariate models. We also stratified the analysis for low-energy reporters only and the associations found remained of similar strength.

Since this is an observational study evaluating a moderate number of participants, it cannot elucidate mechanisms or determine the direction of causality. Although confounding was appropriately controlled for through standard statistical procedures, residual confounding by other serum hormones or unmeasured factors remains a possibility. Dietary intake was evaluated in terms of individual nutrients or food groups; dietary pattern analysis, assessing intercorrelations between dietary variables, would be another alternative for studying interactions between biological indexes and diet. Measurement error in terms of diet and/or determination of hormone levels would result in random misclassification and could have suppressed the relevant effect estimates, but could not have resulted in demonstrating statistical significance. Confirmation of our results by future studies in other population samples, including also men, and assessment of the potential more prolonged effects of diet on both HMW and total adiponectin are warranted.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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